DETAILED ACTION

1. The amendment and RCE filed on 09/18/2009 has been entered and fully considered. Claims 44-61, 63-68, 71, 73 and 74 are pending, of which Claims 44, 63, 71, 73 and 74 are amended.

Response to Amendment

2. In response to amendment, the examiner establishes rejection under 35 U.S.C. 112, and modifies rejection over the prior art established in the previous Office action.

Claim Rejections – 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 44-61, 63-68, 71, 73 and 74 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for reference sample that has substantially the same peptide profile as the first peptide mixture, does not reasonably provide enablement for reference sample that has any peptide profile. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The calculation of the normalization factor is based on the assumption that the reference sample has substantially same peptide profile as the first peptide mixture (see specification page 23, lines 13-14). It would have been an undue experimentation for a routineer in the art to search for a method to calculate normalization factor with any reference sample, as recited in claims 44, 63, 71, 73 and 74.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 44-61, 63-68, 71, 73 and 74 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: calculating normalization factor by excluding all ratios (peptides of analyte to reference) not within the median (0.92) ± the standard deviation (0.42). As disclosed in the specification, this step is essential for the step of comparing the calculated abundance of mass analyzed peptides of the first peptide mixture with an abundance of peptides in a peptide mixture of reference sample, wherein the reference sample is external to the first peptide mixture and the reference sample and the first peptide sample are unlabeled as recited in Claims 44, 63, 71, 73 and 74 (see page 23, lines 11-12).

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. **Claims 44, 47-50, 52, 53, 55, 61, 63-68 and 71** are rejected under 35 U.S.C. 102(b) as being anticipated by Toro et al. (Journal of Chromatography A, 2000) (Toro).

In regard to Claim 44, Toro teaches a method for quantifying peptides in a peptide mixture. The method comprises

receiving a first peptide mixture containing a plurality of peptides (see page 97, left col. 1st paragraph);

separating the plurality of peptide of the first mixture over a period of time (see page 97, left col. 3rd paragraph, right col. 1st paragraph);

mass-to-charge analyzing the separated peptides of the first peptide mixture at a particular time in the period of time (see page 97, left col. 2nd paragraph, right col. 1st paragraph);

calculating an abundance of the mass analyzed peptides of the first peptide mixture (see page 103, Table 5);

calculating a relative quantity for mass analyzed peptides of the first peptide mixture by comparing the calculated abundance of mass analyzed peptides of the first peptide mixture with an abundance of peptides in a reference sample (see page 104, Table 6), wherein the reference sample is external to the first peptide mixture and wherein the reference sample and the first sample peptide mixture are unlabeled (see page 104, Table 6).

In regard to Claims 47 and 48, Toro teaches separating peptides by liquid chromatography, isolating a liquid chromatography eluent at the particular time and mass analysis the isolated eluent (LC-MS) time (see page 97, left col. 3rd paragraph, right col. 1st paragraph).

In regard to Claim 49, Toro teaches identifying peptides in the first sample mixture (see page 101, right col. 2nd and 3rd paragraph).

In regard to Claim 50, Toro teaches identifying the separated peptides based on mass analysis information (see page 101, right col. 2nd and 3rd paragraph).

In regard to Claim 52, Toro teaches reconstructing a chromatogram peak for a peptide based on mass analysis information for the peptide (see page 101, 103 and Figure 3).

In regard to Claim 53, Toro teaches calculating an abundance of a peptide based on a reconstructed chromatogram peak area for the peptide (see page 101, 103 and Figure 3).

In regard to Claim 55, Toro teaches calculating a relative quantity of mass analyzed peptides by comparing an abundance calculated by reconstructing a chromatogram peak area for a peptide of the first peptide mixture with an abundance calculated by reconstructing a chromatogram peak area for a peptide in the reference sample (see page 104, and Table 6).

In regard to Claim 56, Toro teaches normalizing the calculated abundance of mass analyzed peptides of the first peptide mixture (see page 98, right col. 3rd paragraph, Table 2).

In regard to Claim 61, Toro teaches mass-to-charge analyzing and calculating an abundance for arbitrary peptides of the first peptide mixture (see page 103, and Table 5).

In regard to Claim 63, Toro teaches an apparatus for quantifying peptides in a peptide mixture. The apparatus comprises

means for receiving a first peptide mixture containing a plurality of peptides (see page 97, left col. 2nd paragraph);

means for separating the plurality of peptides of the first peptide mixture over a period of time (see page 97, left col. 3rd paragraph);

means for mass analyzing the separated peptides of the first peptide mixture at a particular time in the period of time (see page 97, left col. 2nd paragraph);

means for calculating an abundance of the mass analyzed peptides of the first peptide mixture (see page 98, right col. 2nd paragraph);

means for calculating a relative quantity for mass analyzed peptides of the first peptide mixture by comparing the calculated abundance of the mass analyzed peptides of the first peptide mixture with an abundance of peptides in a reference sample (see page 104, and Table 6); wherein the reference sample is external to the first peptide mixture, the reference sample and the first peptide mixture are unlabeled (see page 104, and Table 6).

In regard to Claim 64, The LC-ESI-MS instrument disclosed by Toro certainly can receive additional sample of peptide mixture (see page 97, left col. 2nd paragraph).

In regard to Claim 65, Toro teaches that the additional peptide mixture comprises a reference sample (see page 98, right col. 2nd paragraph).

In regard to Claim 66, Toro teaches reference information (see page 104).

In regard to Claim 67, Toro teaches mass-to-charge analyzing and calculating an abundance for arbitrary peptides of the first peptide mixture (see page 103 and 104).

In regard to Claim 68, Toro teaches separating, mass-to-charge analyzing and calculating an abundance for peptides independent of a particular amino acid composition of the subject peptides (see page 103, 104).

In regard to Claim 71, Toro discloses an apparatus for quantifying peptides in a first peptide mixture. The apparatus comprises digital circuitry configured to perform the following actions:

receiving separation information representing a separation of a plurality of peptides of a first peptide mixture over a period of time (see page 97, left col. 3rd paragraph);

receiving mass-to-charge analysis information for the separated peptides of the first peptide mixture at a particular time in the period of time (see page 97, left col. 2nd paragraph, page 101, right col. 3rd paragraph and Table 4);

calculating an abundance of the mass analyzed peptides of the first peptide mixture (see page 103); and

calculating a relative quantity for the mass analyzed peptides of the first peptide mixture by comparing the calculated abundance of the mass analyzed peptides of the first peptide mixture with an abundance of the peptides in a reference sample, the reference sample being external to the first peptide mixture (see page 103 and 104 and Table 6); wherein the reference sample and the first peptide mixture are unlabeled.

Claim Rejections - 35 USC § 103

9. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

10. **Claims 45, 46, 51, 54, 56-60, 73 and 74** are rejected under 35 U.S.C. 103(a) as being unpatentable over Toro in view of Aebersold et al. (Chemical Review, 2001) (Aebersold).

In regard to Claims 45 and 46, Toro teaches calculating an abundance of peptides in the second peptide sample and calculating relative quantity for the mass analyzed peptides of the first peptide mixture by comparing the calculated abundance of mass analyzed peptides of the first peptide mixture with the calculated abundance of corresponding mass analyzed peptide from the second polypeptide sample (see page 103 and 104, and Table 6). Toro does not teach digesting a first polypeptide sample or a second peptide sample. Aebersold teaches that the accurate mass of a group of

peptides derived from a protein by sequence-specific proteolysis is a highly effective means of protein identification (see page 273, left col. 2nd paragraph). At the time of the invention it would have been obvious to one of ordinary skill in the art to digest polypeptide sample to generate smaller peptide for mass spectrometry analysis, because Aebersold teach that smaller peptide allows more accurate mass measurement by mass spectrometry.

In regard to Claim 51, Toro does not teach teaches fragmenting an ion derived from a peptide of separated peptides. Aebersold teaches fragmenting an ion derived from a peptide of separated peptides and mass analyzing fragments of the ion (LC-MS/MS) and identifying peptides in the first sample by searching a sequence database based on mass analysis information for the fragments (see page 276, right col.). At the time of the invention it would have been obvious to one of ordinary skill in the art to use LC-MS/MS for peptide analysis, because Aebersold teaches that the low-energy CID spectra of peptides generated by ESI-MS/MS are of high quality and are sequence specific (see page 276, right col. 2nd paragraph).

In regard to Claim 54, Toro does not specifically teach using only chromatogram peaks located within a threshold distance in the reconstructed chromatogram of the particular time. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). In that regard, it is well know in chromatography that each eluent peak has a retention time that corresponds to its peak intensity. Therefore, it would have been obvious to a person of ordinary skill in the art to run MS analysis at the retention time that is as close to the peak retention time as possible in order to obtain the highest intensity of MS chromatogram. The optimum threshold distance from the peak retention time can be obtained by routine experimentation.

In regard to Claim 57, Toro does not teach normalizing the calculated abundance of mass analyzed peptides of the first peptide based on an internal standard that is added to the first polypeptide sample. Aebersold teaches adding internal standard to peptide sample to quantify the peptides in the sample (see page 284, left col. 2nd

paragraph). At time of the invention it would have been obvious to one of ordinary skill in the art to add internal standard to the peptide sample for quantifying the peptide in the sample under the same condition.

In regard to Claim 58, Toro teaches normalizing the calculated abundance based on an external standard (see page 103 and 104 and Table 6).

In regard to Claim 59, Toro teaches identifying a plurality of peptides of the first peptide mixture based on the mass analysis and calculating a relative quantity for each of the identified peptides (see page 103, 104).

In regard to Claim 60, Toro teaches that the relative quantification is determined by the ratio of reconstructed chromatogram peak area of the peptide pairs (see page 103, 104). Toro does not specifically teach calculating a single correction factor for a set of peptides in the first peptide mixture. However, when correction factors are calculated for each of the peptides in the first peptide mixture, a single correction factor for the peptide set in the first peptide mixture can be calculated in a similar way based on a single reference. It would have been obvious to a person of ordinary skill in the art to calculate a single correction factor for the peptide set in the first peptide mixture based on a single reference in a same way as taught by Toro.

In regard to Claims 73 and 74, Toro teaches a method and apparatus for quantifying peptides in a biological sample. Toro does not specifically teach that the method and apparatus can also be used for quantifying compounds in a biological sample. The court has held that a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim (see MPEP 7.37.09). In that regards, the processes and apparatus recited in the instant claims can be derived from Toro's teaching by simply substituting peptide with the compound. At the time of the invention it would have been obvious for a person of ordinary skill in the art to use Toro's method and apparatus for quantifying compound in a biological sample.

Response to Arguments

11. Applicant's arguments with respect to claims 44, 63, 71 and 73-43 have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ROBERT XU whose telephone number is (571)270-5560. The examiner can normally be reached on Mon-Thur 7:30am-5:00pm, Fri 7:30am-4:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Vickie Kim can be reached on (571)272-0579. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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